Oligomerization of Vinyl Monomers. 17. Stereoselective Methylation of 1-Lithio-1,3-bis(phenylsulfinyl)butane. Kinetic vs. Thermodynamic Control in the Formation of Diastereomeric Ion Pairs

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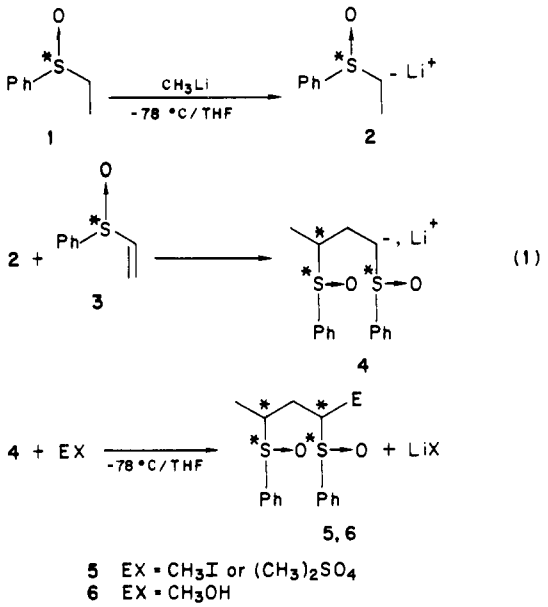
Abstract: The addition of (*R*)- or (*R,S*)-vinyl phenyl sulfoxide (**3**) to (*R*)- or (*R,S*)-1-lithio-1-(phenylsulfinyl)ethane (**2**) was carried out in THF at −78 °C, and the adduct anion **4** was protonated or methylated to produce 1,3-bis(phenylsulfinyl)butane (**6**) or 2,4-bis(phenylsulfinyl)pentane (**5**). The stereochemistry of methylation was shown to strongly depend upon the **3**/**2** ratio and the method of preparation of Li-**4**, including its thermal treatment prior to methylation (CH_3I or $(CH_3)_2SO_4$) at −78 °C. The results are shown to be consistent with the existence of ion pair diastereomers of **4** that do not measurably interconvert at −78 °C but equilibrate at temperatures between 0 and 55 °C.

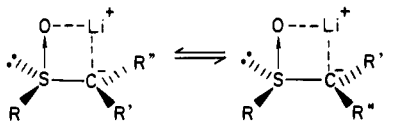
We have recently reported the dimerization of vinyl phenyl sulfoxide[1] (**3**) initiated by 1-lithio-1-(phenylsulfinyl)ethane (**2**) (eq 1). This reaction occurred with the preferential addition of (*R*)-**2** to (*S*)-**3** (92%) and the stereoselective formation of the *S* chiral center α to the (*R*)-sulfinyl group (>98%).[2] Due to the



high stereoselectivity of the reaction, only two of the four diastereomeric protonated dimers (**6**) could be isolated from the oligomeric mixture. Likewise only four of the six diastereomeric dimers (**5**) (Figure 1) could be isolated.

In this paper we report the synthesis and stereochemical characterization of the six diastereomers of **5**. Different ratios

Scheme I

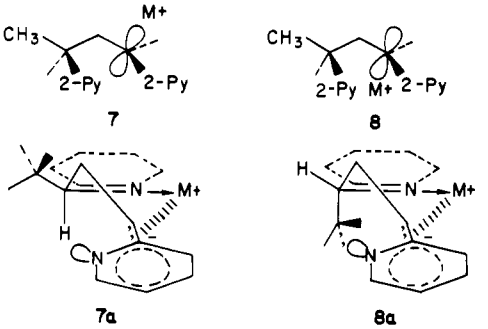


of the four diastereomers of **5** resulting from vinyl addition and methylation could be isolated depending upon the average degree of oligomerization, optical purity of the reactants, **1** and **3**, and upon the time–temperature profile of the intermediate carbanion solution. These differences will be interpreted by a model involving diastereomeric ion pairs of **4**, with the ratio of the diasteriomers of **5** being controlled either kinetically or thermdynamically.

At low temperatures in tetrahydrofuran, α-sulfinyl carbanions have been shown to be sp^2-hybridized[3] and to exist as tight ion paris[3b,4] in which the carbanion is stabilized by the S → O dipole. Such an arrangement should lead to the formation of diastereomeric ion pairs (Scheme I), of which the rate of interconversion is dependent on the counterion,[5] the temperature,[5] the solvent, and the structure of the carbanion.

The presence of a sulfinyl group γ to the carbanion in **4** allows additional intramolecular coordination of the metal ion which may strongly influence its stereochemistry. For example, the analogous 1-lithio-1,3-di(2-pyridyl)butane undergoes a highly stereoselective methylation in THF leading to the mesoisomer.[6]

These results were shown to be consistent with a chelated structure **7a** corresponding to ion pair **7**. Such a structure is expected to be favored over structure **8a** (corresponding to ion



(1) Buese, M. A.; Hogen-Esch, T. E. *Macromolecules* **1984**, *17*, 118.

(2) Sulfur chirality is indicated by a subscript S in our notation. The first sulfur configuration listed was derived from **1**, the first carbon configuration listed was formed by vinyl addition, and the second by methylation. Thus, the reaction which led to (R_S,*S*,*R*,R_S)-**5** and (R_S,*S*,*S*,R_S)-**5** also yielded (R_S,*S*,R_S)-**6** upon protonation. Isomers in the first row (Figure 1) are "meso" compounds with a mirror plane defined by the methylene carbon and hydrogens. All other isomers are one of a pair of enantiomers. The second row contains "racemic" isomers containing a 2-fold proper rotation axis bisecting the H–C–H bond angle of the methylene group. When optically enriched **1** and **3** were used, it is indicated. In those cases, the dimers formed are also enriched in the enantiomers pictured in Figure 1. When no sign of rotation is indicated, a racemic mixture of the reagents was used and it should be understood that (R_S,*S*,*S*,S_S)-**5** are relative configurations with both enantiomers present in equal quantities. Where ambiguity may arise, the word "rel" precedes the Kahn–Ingold notation to indicate a racemic mixture.

(3) (a) Lett, R.; Marquet, A. *Tetrahedron Lett.* **1975**, *19*, 1579. (b) Lett, R.; Chassaing, G.; Marquet, A. *J. Organomet Chem.* **1976**, *111*, C17.

(4) Nighi, S.; Matsuda, M. *J. Am. Chem. Soc.* **1979**, *101*, 4632.

(5) Chassaing, G.; Marquet, A.; Corset, J.; Froment, F. *J. Organomet Chem.* **1982**, *4*, 293.

(6) Huang, S. S.; Mathis, C.; Hogen-Esch, T. E. *Macromolecules* **1981**, *14*, 1802. Hogen-Esch, T. E.; Tien, C.-F. *Macromolecules* **1980**, *13*, 207.

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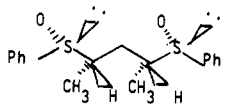
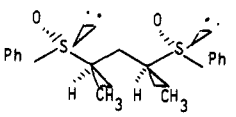
Table I. Proton and ^{13}C Chemical Shifts of All Stereoisomers of Dimer **5**

	^{13}C (25 MHz)[a]			^{1}H (400 MHz)		
	CH_3	CH_2	CH	CH_3	CH_2	CH
			5			
(R_S,S,S,S_S)	10.6, 13.8	30.6	56.4, 56.6	0.89, 1.13[b]	1.84,[b] 1.90[b]	2.74,[b] 3.00[b]
(R_S,S,S,R_S)	10.8	31.8	56.0	1.04	1.94	2.8
(R_S,R,R,R_S)	12.8	28.0	56.4			
(R_S,S,R,S_S)	10.4	33.0	56.2	1.04	1.77, 2.47	2.89
(R_S,S,R,R_S)	11.2, 14.1	29.7	56.2, 56.4	0.96, 1.31[b]	1.51, 2.13	2.80, 3.04
(R_S,R,S,S_S)	14.0	30.0	56.0			
			6			
(R_S,S,S_S)	10.0	23.7 53.5	57.6	0.92[b]	1.81, 2.88[b]	2.70[b]
(R_S,S,R_S)	10.2	23.0 52.9	57.4	0.93[c,d]	2.28, 2.95[b]	

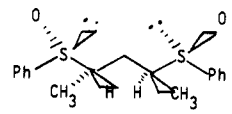
[a] In $CDCl_3$. [b] 300 MHz. [c] 100 MHz. [d] (R_S,S,R_S)-**6** was never in pure form, and the methine signals were not resolved from those of (R_S,S,S_S)-**6**.



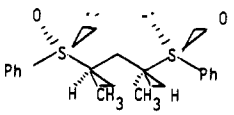
(R_S,S,R,S_S)-**5**



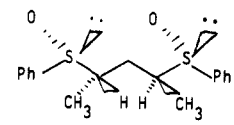
(R_S,R,S,S_S)-**5**



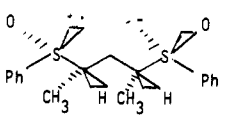
(R_S,S,S,R_S)-**5**



(R_S,R,R,R_S)-**5**



(R_S,S,S,S_S)-**5**



(R_S,S,R,R_S)-**5**

Figure 1. Diastereoisomers of dimer **5**.[2]

pair **8**) on account of nonbonded interactions and a butane gauche interaction in **8a**. Methylation of **7** occurs syn to the cation and results in the formation of *meso*-2,4-di(2-pyridyl)pentane in 99% diastereomeric purity.[7]

We will show that the methylation stereochemistry of **4** can similarly be explained by a six-membered ring formed by intramolecular coordination of the lithium ion. We shall also demonstrate that the methylation stereochemistry is consistent with the cation side methylation of the diastereomeric ion pairs of **4** of which the relative proportions are determined either by kinetic or thermodynamic control.

Experimental Section

Tetrahydrofuran was distilled from a Na/K alloy with benzophenone indicator on a vacuum line. Methylating agents were purified by distillation from CaH_2. Methyllithium (low halide) was purchased from Aldrich.

Synthesis of (+)-1. A solution of *l*-menthol (Aldrich) in pyridine was added dropwise to benzenesulfinyl chloride[7] in ether to give a mixture of diasteriomeric sulfinate esters.[8] Two recrystallizations from methanol and three from hexane yielded white needles of *l*-1-menthylbenzene sulfinate: mp 49.5–50 °C (lit.[8] mp 49–51 °C)[8]; $[\alpha]^{25}_D$ −202° (acetone). Using Andersen's method,[9] (+)-**1** resulted from the addition of ethylmagnesium iodide in ether to the sulfinate ester in ether. The crude sulfoxide was flash-chromatographed[10] on a 15 × 4 cm 400-mesh silica gel column with a 5:1 hexane/acetone mixture to separate *l*-menthol from (+)-**1**. The sulfoxide was dried over CaH_2 and distilled twice from CaH_2 at 80–82 °C at 1 × 10^{-2} mmHg with the product of the second distillation collected in a tube equipped with a breakseal which was then sealed under vacuum. An isolated yield of 35% from the sulfinate ester was obtained: $[\alpha]^{25}_D$ +194° (acetone); ^1H NMR (acetone-d_6) δ 7.6 (5 H), 2.88 (ABX_3, 1 H), 2.70 (ABX_3, 1 H J_{AB} = 13.8 Hz, J_{AX} = J_{BX} = 7.2 Hz), 1.09 (3 H, J = 7.2 H_z); ^{13}C NMR (acetone-d_6) δ 146.5 (1 C, 132.2 (2 C), 130.8 (1 C), 126.1 (1 C), 51.4 (1 C), 6.7 (1 C); IR (NaCl dish) 3060 (m), 2980 (m), 2940 (m), 2880 (w,) 1480 (m), 1442 (s), 1085 (vs), 1070 (m), 1042 (vs), 1020 (vs), 745 (s), 690 (s) cm^{-1}.

Synthesis of (±)-1. Racemic **1** was synthesized as was (+)-**1** by using (±)-ethylbenzene sulfinate rather than *l*-1-menthylbenzene sulfinate. No flash chromatography was needed prior to distillation. A 40% yield of colorless sulfoxide was obtained.

Synthesis of (+)-3. The synthesis and purification of (+)-**3** was analogous to that of (+)-**1** when using vinylmagnesium bromide in THF rather than ethylmagnesium iodide in ether. A 35% yield of colorless (+)-**3** was obtained by distillation at 83–6 °C at <1 × 10^{-2} mmHg, $[\alpha]^{25}_D$ +474° (acetone).

Racemic **3** was purchased from Aldrich and purified in the same way as (+)-**3**.

Dimerization. One equivalent of **1** was added to methyllithium in THF at −78 °C under vacuum in a flask equipped with a breakseal. When the resulting yellow solution no longer generated methane gas, the flask was sealed. When high vacuum techniques were used, **2** in THF at −78 °C was mixed rapidly with **3** in THF at −78 °C to form **4**. Methylated or protonated oligomers were formed by the addition of a large excess of methyl iodide, dimethyl sulfate, or methanol to the reaction mixture at −78 °C. Dimers were isolated by liquid chromatography by using an Altex Model 110A chromatograph, a Lobar "B" LiChroprep Si 60(40–63 μm) column, and a 254-nm UV detector. A programmed elution from 100% hexane to 40% hexane, 60% 10:1 methylene chloride/methanol, during a 400-min period, was generally used. Analyis by NMR spectroscopy was carried out on a JEOL FX100 (100-MHz ^1H and 25-MHz ^{13}C), a Nicolet NT-300 (300-MHz ^1H), or a Brucker WP-400 (400-MHz ^1H). White needles (mp 107–108 °C (R_S,S,R_S,S)-**5** were recrsytallized from acetone/H_2O.

Preparation of *rel*-(R_S,S,S,S_S)-4 from *rel*-(R_S,S,S,S_S)-6.[2] Isolated *rel*-(R_S,S,S,S_S)-**6** was weighed in a flask equipped with a filter and breakseal. The flask was evacuated and the *rel*-(R_S,S,S_S)-**6** was dissolved in THF, dried over CaH_2, filtered into the side of the flask containing the breakseal and then sealed under vacuum. The solution was cooled to −78 °C and added from the breakseal to a THF solution of methyllithium at −78 °C under vacuum. Methylation was carried out at −78 °C by distilling an excess of methyl iodide onto the carbanion solution.

Epimerization of 5. Epimerization of **5** was carried out by racemization of the sulfinyl groups.[11] A mixture of 0.1 g of *rel*-(R_S,S,S,S_S)-**5** or (R_S,S,R,S_S)-**5**, 5 mL of 12 N HCl, and 10 mL of dioxane were stirred for 24 h and then extracted with two 10-mL portions of ether. The residue from ether was flash-chromatographed with a 3:1 hexane/acetone mixture on a 15 × 1 cm 400-mesh silica gel column. Evaporation of the eluting solvent yielded the epimerized dimer mixture.

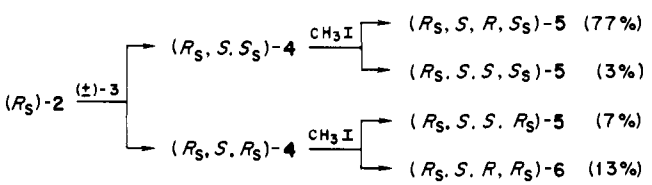
(7) Douglas, I. B.; Norton, R. V. *J. Org. Chem.* **1968**, *33*, 2104.
(8) Herbrandson, H.; Dickerson, R. T., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 4102.
(9) Andersen, K. K. *Tetrahedron Lett.* **1962**, *3*, 93.
(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(11) Mislow, K.; Simmons, T.; Mellelo, J. T.; Ternay, A. L., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 1452.

Table II. Stereochemistry of Methylation (CH_3I) of the Lithium Salt of Anion **4** at −78 °C in THF as a Function of Concentration and Enantiomeric Composition of Carbanion **2** and Vinyl Sulfoxide **3**[a]

run	$[\alpha]^{25}_D$ **1**	**3**	**3/2**	**2**, mol/L	(R_S,*S*,*R*,S_S)-**5**/(R_S,*S*,*S*,S_S)-**5**	(S_S,*S*,*R*,R_S)-**5**/(R_S,*S*,*S*,R_S)-**5**
1	0	0	0.5	5×10^{-2}	0.48	
2	0	0	1.0	5×10^{-2}	0.55[b]	
3	0	0	1.0	5×10^{-2}	0.71[c]	
4	0	0	1.0	2×10^{-1}	0.55	
5	0	0	~1	6×10^{-4}	0.67	
6	0	0	2.0	5×10^{-2}	>20	
7	+194°	0	1.0	5×10^{-2}	>25	1.9
8	+146°	+446°	0.5	5×10^{-2}		0.28
9	+146°	+446°	1.0	5×10^{-2}		2.6
10	*d*	*d*	*d*	2×10^{-2}	>20	

[a] Methylation at −78 °C by addition of CH_3I (10 times excess). [b] Methylated 15 min after mixing **2** and **3**. [c] Methylated 90 min after mixing **2** and **3**. [d] Anion **4** generated by deprotonation of *rel*-(R_S,*S*,S_S)-**6** at −78 °C in THF with CH_3Li.

Scheme II



Results

Stereochemistry of Dimer Formation. The reaction mixture from (*R*)-(+)-**2** with 1 equiv of (±)-**3** was divided into three portions of −78 °C. One part was protonated, another methylated by CH_3I. Two diastereomers of **6** were produced upon protonation in an 80:20 ratio. Four diastereomers of **5** were produced in a 77:3:7:13 ratio.

The major stereoisomer of **5** was a meso isomer according to the ^1H NMR spectrum which exhibited equivalent methyl and methine signals and an ABX_2 pattern for the methylene protons (Table I). Single-crystal X-ray analyses confirmed that this meso isomer was (R_S,*S*,*R*,S_S)-**5** and not (R_S,*R*,*S*,S_S)-**5**.[1] Thus, the predominant protonated dimer was (R_S,*S*,S_S)-**6**. The minor (3%) isomer of **5** was unsymmetrical by inspection of both ^1H and ^{13}C NMR spectra and was tentatively assigned to (R_S,*S*,*S*,S_S)-**5** since 80% of both mixtures had to result from (R_S,*S*,S_S)-**4**.

The third most abundant stereoisomer of **5** exhibited equivalent methyl and methine carbons and equivalent methylene protons, indicating a "racemic" isomer. The two sulfur atoms in this isomer should therefore have the *R* configuration [(R_S,*S*,*S*,R_S)-**5** or (R_S,*R*,*R*,R_S)-**5**)]. This indicates in turn that the apparent stereoselectivity of vinyl addition with respect to the sulfur configuration of **3** is not high. Thus, the two isomers of **4** are most likely (R_S,*S*,S_S)-**4** and (R_S,*S*,R_S)-**4**, the addition reaction being highly stereoselective with respect to the formation of the chiral carbon.[12] The third abundant stereoisomer of **5** is therefore (R_S,*S*,*S*,R_S)-**5**. The second most abundant (13%) isomer was found to be unsymmetrical, and its stereochemistry therefore was (R_S,*S*,*R*,R_S)-**5** (Scheme II). The ^1H and ^{13}C methyl signals for both isomers of **6** were similar in chemical shift, again suggesting the same configuration of the chiral carbon. Furthermore, the ^1H and ^{13}C chemical shifts of the methyl group corresponding to **2** in all four isomers of **5** were similar, confirming the assignments. The chemical shifts of the other CH_3 signals (corresponding to methylation) of the two assymetrical isomers (R_S,*S*,*R*,R_S)-**5** and (R_S,*S*,*S*,S_S)-**5** were found to be similar, again consistent with the above assignments. These assignments are also supported by acid-catalyzed epimerization of (R_S,*S*,*S*,R_S)-**5**. The (S_S,*S*,*S*,S_S)-**5** isomer formed in this reaction had a methyl ^{13}C absorption about 2 ppm downfield from that of (R_S,*S*,*S*,R_S)-**5** and approximately the same as the downfield CH_3 absorption of (R_S,*S*,*S*,S_S)-**5**. Likewise the epimerization of (R_S,*S*,*R*,S_S)-**5** lead to the other meso isomer, (R_S,*R*,*S*,S_S)-**5**, the ^{13}C methyl of which absorbed downfield of that of (R_S,*S*,*R*,S_S)-**5**.

Methylation Stereochemistry of 4. The stereoisomeric composition of **5**[13] was strongly dependent upon the method of preparation of **4**. As previously reported,[1] the ratio of (R_S,*S*,R_S)-**6** to (R_S,*S*,S_S)-**6** depended upon the optical purity and the molar ratio of the compounds **2** and **3**. This dependence on optical purity and stereochemistry was also observed for the methylation of (R_S,*S*,S_S)-**4** and (R_S,*S*,R_S)-**4**. As the **3**/**2** molar ratio increased for the reaction between (±)-**2** and (±)-**3**, the ratio (R_S,*S*,*R*,S_S)-**5**/(R_S,*S*,*S*,S_S)-**5** increased rapidly (runs 1–6, Table II). Also, for the reaction of (+)-**2** with (+)-**3**, the ratio (R_S,*S*,*R*,R_S)-**5**/(R_S,*S*,*S*,R_S)-**5** increased 10-fold as the (+)-**3**/(+)-**2** ratio increased 2-fold (runs 8 and 9, Table II). These variations were not related to carbanion concentration (runs 2–5, Table II) because a 300-fold variation in carbanion concentration produced no significant change. When *rel*-(R_S,*S*,S_S)-**4** was generated by the lithiation of *rel*-(R_S,*S*,S_S)-**6**, only (R_S,*S*,*R*,S_S)-**5** was formed upon subsequent reaction with methyl iodide (run 10, Table II). No epimerization of the methine carbon or formation of *rel*-1,3-(1*S*,3*R*)-bis(phenylsulfinyl)-3-methylbutane was observed.

The temperature–time profile of the solution of **4** also affected the observed methylation stereochemistry. The formation of **4** is complete within 5 min of mixing (±)-**2** and (±)-**3**.[13,14] After an additional 15 min, the reaction mixture was separated into two portions. One portion was maintained at −78 °C for an additional 80 min and then methylated. The other portion was transferred to a 0 °C bath for 60 min and then placed in the −78 °C bath for 20 min prior to methylation at that temperature. A 10-fold difference in the (R_S,*S*,*R*,S_S)-**5**/(R_S,*S*,*S*,S_S)-**5** ratio for the two portions was observed (runs 1a and 1b, Table III). Under these conditions, the (R_S,*S*,*R*,R_S)-**5**/(R_S,*S*,*S*,R_S)-**5** was the same as that of the portion kept at −78 °C (runs 4a and 4b, Table III). However, when the sample was heated at 55 °C rather than 0 °C, a large difference in the (R_S,*S*,*R*,R_S)-**5**/(R_S,*S*,*S*,R_S)-**5** ratio was observed relative to the portion kept at −78 °C (runs 5a and c, Table III).

It has been claimed in similar systems that the methylation of α-sulfinyl carbanions occurs "syn" to the cation with dimethyl sulfate and "anti" with methyl iodide.[15] Thus, (±)-**3** and 2 equiv of (±)-**2** were mixed, the resulting solution was divided into two portions, and one part was methylated at −78 °C with methyl iodide and the other with dimethyl sulfate. The *rel*-(R_S,*S*,*R*,S_S)-**5**/*rel*-(R_S,*S*,*S*,S_S)-**5** ratio from the dimethyl sulfate portion was nearly the inverse of that for methyl iodide (runs 2a and 2b, Table III). However, the reaction of **4** with dimethyl sulfate was much slower than that with methyl iodide. Thus, the yellow color

(12) Methyl groups β to sulfinyl groups are generally very sensitive to stereochemistry; see for example: Kingsbury, C. A.; Day, V. W.; Day, R. O. *J. Org. Chem.* **1980**, *45*, 5225 and references sited therein.

(13) The two ^{13}C NMR signals for the methyls of (R_S,*S*,*S*,S_S)-**5**, and likewise (R_S,*S*,*R*,R_S)-**5**, were found to be of equal intensity. Also the ratio of isomers calculated from their ^{13}C NMR methyl signal intensities agreed well with the ratios calculated from the ^1H NMR spectra. Thus, the NOE's of diastereomeric methyl groups are equal and were used to determine ratios of the various stereoisomers.

(14) No. **3** could be recovered from the reaction mixture from **2** and 1 equiv of **3** when protonated 5 min after mixing **2** and **3** at −78 °C.

(15) Biellmann, J. F.; Vicens, J. J. *Tetrahedron Lett.* **1978**, *5*, 469.

Table III. Stereochemistry of Methylation of the Lithium Salt of Anion **4** as a Function of the Temperature–Time Profile of the Solution and the Nature of the Leaving Group

run	$[\alpha]^{25}_D$ 1	3	3/2	T_{max}[a] °C	CH_3X	(R_S,S,R,S_S)-**5**/ (R_S,S,S,S_S)-**5**	(R_S,S,R,R_S)-**5**/ (R_S,S,S,R_S)-**5**
1a	0	0	1.0	−78[b]	CH_3I	0.70	
1b	0	0	1.0	0[b]	CH_3I	8.0	
2a	0	0	0.5	−78[c]	CH_3I	0.47	
2b	0	0	0.5	−78[c]	$(CH_3)_2SO_4$	2.2	
3a	0	0	1.0	0[e]	CH_3I	8.0	
3b	0	0	1.0	0[e]	$(CH_3)_2SO_4$	8.0	
4a	+146	+446	1.0	−78[b]	CH_3I	1.3	2.6
4b	+146	+446	1.0	0[b]	CH_3I	9.0	2.5
5a	+146	+446	0.55	−78[d]	CH_3I	1.0	0.30
5b	+146	+446	0.55	−78[d]	$(CH_3)_2SO_4$	1.0	0.30
5c	+146	+446	0.55	55[b]	CH_3I	10	10

[a] Highest temperature of the carbanion solutions before methylation. [b] Addition reaction at −78 °C. Solution was divided into two parts. One was kept at −78 °C throughout; the other was warmed to 0 °C, (or 55 °C, run 5c)8 kept at that temperature for 60 min, recooled to −78 °C for 20 min, and methylated at −78 °C. [c] Kept at −78 °C for 20 min, followed by addition of CH_3I, kept at −78 °C for 18 h, and removed from the cold bath. [d] After 2 at −78 °C, the methylating agent was added, and the solution was removed from the cold bath. [e] As in *b* with both portions warmed to 0 °C.

of the carbanion solution disappeared within 4 h following the addition of methyl iodide but persisted for more than 18 h after the addition of dimethyl sulfate. It appeared, therefore, that the difference in methylation was perhaps not due to differences in the mode of methylation but was rather a consequence of the different rates of methylation. Thus, when two portions of a solution of **4** were warmed to 0 °C for an hour, rechilled to −78 °C, and then methylated with methyl iodide and dimethyl sulfate, respectively, no difference in the product ratio was observed (runs 3a and 3b, Table III). Analogous results were observed for the methylation of (R_S,S,R_S)-**4** by methyl iodide and dimethyl sulfate when the portions were removed from the −78 °C bath and allowed to warm to room temperature immediately after addition of the methylating agents (runs 5a and b, Table III). Loss of the yellow color occurred within 5 min for both methylating agents.

Discussion

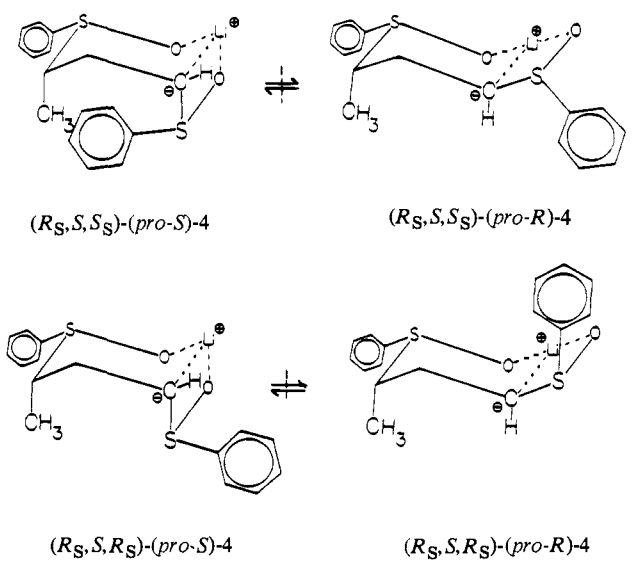
A description of the observed stereochemistry of methylation of **4** must account for the differences in stereochemistry due to the varying ratios of **2** and **3** and the dependence upon the time–temperature profile of the reaction.

Explanation of the observed stereochemistry based on ionic equilibria is not plausible. Measurements of the UV spectra of monomeric sulfinyl carbanions indicate the presence of tight ion pairs.[4] Conductance measurements of THF solutions of **2** show the virtual absence of free ions.[16] Although aggregation of **4** is possible,[17] it does not seem relevant to methylation as indicated by the absence of effects due to carbanion concentration (runs 2–5, Table II). Furthermore, it is difficult to rationalize the pronounced effects on the stereochemistry of methylation of the time–temperature profile on the basis of ionic aggregation.

An explanation based upon ion pairs of **4** seems to be most reasonable. In this case, a strong intramolecular coordination of Li by the penultimate highly polar sulfinyl group[18] is likely.

In ion pairs (R_S,S,S_S)-**4** and (R_S,S,R_S)-**4**, the counterion may be present at either of the two prochiral faces of the carbanion, i.e., *pro-S* and *pro-R*. The Li ion, moreover, is expected to be coordinated by the α-sulfinyl group. These interactions are expected to appreciably slow the rates of interconversion of the *pro-S* and *pro-R* forms of the two isomeric anions. Furthermore, the (R_S,S,S_S)-(*pro-R*)-**4** structure should be more stable than (R_S,S,S_S)-(*pro-S*)-**4** due to the 1,3-diaxial interaction between the methyl and the phenylsulfinyl groups of (R_S,S,S_S)-(*pro-S*)-**4** (Scheme III). This is also expected to be the case for (R_S,S,R_S)-(*pro-S*)-**4** and (R_S,S,R_S)-(*pro-R*)-**4**, the latter being more stable. The difference between these *pro-R* and *pro-S* diasteromers is expected to be less than the difference for the corresponding forms of (R_S,S,S_S)-**4**, however, due to highly unfavorable interactions present in (R_S,S,S_S)-(*pro-S*)-**4**. The interconversion between the two ion pair diasteroisomers is thus expected to be more rapid in the case of (R_S,S,S_S)-**4**. The alternative conformation containing an axial position of the phenyl group is expected to be inconsistent with the order of ease of interconvertibility of the ion pair diastereomers. Our results appear to be consistent with these observations. Thus, at −78 °C, the stereochemistry is dominated by the relative kinetic preference for the *pro-R* and *pro-S* forms, the methylation always occurring cation side (syn). At higher temperatures, the thermodynamic stabilities of the various ion pair diastereoisomers prevail. Thus at 0 °C, the thermodynamically less stable (R_S,S,S_S)-(*pro-S*)-**4** is transformed into the more stable *pro-R* form resulting in the predominant formation of (R_S,S,R,S_S)-**5**. At 55 °C, the corresponding transformation of (R_S,S,R_S)-**4** results in predominantly (R_S,S,R,R_S)-**5**.

Scheme III



Kinetic control varies with the stoichiometry of reactants and their optical purity as it reflects not only the rate of formation of the diasteromers of **4** but also their depletion by subsequent vinyl addition to form trimer. Thus, (R_S,S,S_S)-(*pro-S*)-**4** may be formed preferentially (~2:1) over (R_S,S,S_S)-(*pro-R*)-**4** (run 1, Table II). Likewise, (R_S,S,S_S)-(*pro-S*)-**4** is formed about 2.5 times as rapidly as (R_S,S,R_S)-(*pro-R*)-**4** (run 8, Table II). Apparently the reaction of **3** with **4** preferentially depletes the less stable (R_S,S,S_S)-(*pro-S*)-**4** and (R_S,S,R_S)-(*pro-S*)-**4** isomers. Thus, the ratios (R_S,S,S_S)-(*pro-R*)-**4**/(R_S,S,S_S)-(*pro-S*)-**4** and (R_S,S,R_S)-(*pro-R*)-**4**/(R_S,S,R_S)-(*pro*-S)-**4** increase as the **3**/**2** ratio increases. Those solutions maintained at −78 °C for very long periods of time before methylation also reflect the rate of

(16) Buese, M. A.; Hogen-Esch, T. E., unpublished results.
(17) Chassaing, G.; Marquet, A. *Tetrahedron* **1978**, *34*, 1399.
(18) Toshiyasu, Y.; Taniguchi, Y.; Kimura, K.; Fujishiro, R.; Yoshiharo, M.; Tagaki, W.; One, S. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1878.

equilibration of the diastereomeric ion pair forms.[19] Hence methylation by dimethyl sulfate at −78 °C is so slow that equilibration can proceed to a significant extent (run 2b, Table III).

The above effects, in particular the effects of reaction stoichiometry and the temperature–time profile of the reaction, have not been observed in the analogous dimerization reactions involving the addition of α-lithio-2-ethylpyridine to 2-vinylpyridine in THF followed by methylation.[7] These reactions resulted in the stereoselection formation of *meso*-2,4-di(2-pyridyl)butane (>99% at −78 °C) and were found to be only dependent on the temperature of methylation. As seen in **7a** and **8a**, coordination of the metal ion by the lone pair of the penultimate nitrogen atom brings about a difference in stability of the two diastereomeric ion pairs with ion pair **7** being strongly favored over **8**. Attempts to differentiate between **7** and **8** by NMR techniques[20] have failed, presumably as a result of their rapid interconversion.

In conclusion, the methylation stereochemistry of **4** is dependent upon the method of generation of the carbanion, the stoichiometry and optical purity of **2** and **3**, and the time–temperature profile of the carbanion solution. In most cases, it reflects the relative rates of formation, depletion, and slow interconversion of the diastereomeric ion pairs. If one warms the carbanion solution, the interconversion of the *pro-R* and *pro-S* diastereomeric ion pairs becomes rapid, and upon cooling the thermodynamic mixture is frozen out. Thus, the methylation stereochemistry can be determined either kinetically or thermodynamically by controlling the time–temperature profile of the carbanion solution and the stoichiometry and optical purity of the reagents.

(19) Such effects for monomeric sulfinyl carbanions have been observed. Solladie, G.; Zimmerman, R.; Bartsch, R. *Tetrahedron Lett.* **1983**, *24*, 755.
(20) Tien, C. F.; Hogen-Esch, T. E., unpublished results.

Acknowledgment. Support by the National Science Foundation, Division of Materials Research, Polymers Program, is gratefully acknowledged. We also acknowledge the use of the Chemistry Department Nicolet NT-300 NMR spectrometer supported by the instrument program of the NSF Chemistry Division. Thanks are also due to Dr. R. Sheardy (University of Rochester, Rochester, NY) for his help in obtaining the 400-MHz NMR spectra, and to Dr. G. Palenik and Dr. V. Lynch (University of Florida) for the X-ray data.

Registry No. (*R*)-(+)-**1**, 51207-25-1; (±)-**1**, 67529-33-3; (±)-**2**, 96614-05-0; (*R*)-(+)-**2**, 88180-52-3; (*R*)-(+)-**3**, 89299-86-5; (±)-**3**, 88180-53-4; (±)-(*R,S,S*)-**4**, 96556-01-3; (±)-(*R,S,R*)-**4**, 96614-06-1; *meso*-(*R,S,R,S*)-**5**, 96614-09-4; (±)-(*R,S,S,S*)-**5**, 96614-10-7; (±)-(*R,S,S,R*)-**5**, 88243-86-1; (±)-(*R,S,R,R*)-**5**, 96614-11-8; (±)-(*R,R,R,R*)-**5**, 96646-21-8; *meso*-(*R,R,S,S*)-**5**, 88180-51-2; (±)-(*R,S,S*)-**6**, 96614-07-2; (±)-(*R,S,R*)-**6**, 96614-08-3; (*l*)-menthol, 2216-51-5; benzenesulfonyl chloride, 4972-29-6; (*l*)-1-menthylbenzene sulfinate (isomer 1), 34513-32-1; (*l*)-1-menthylbenzene sulfonate (isomer 2), 96614-12-9; ethylmagnesium iodide, 10467-10-4; (±)-ethyl benzenesulfonate, 96556-00-2; vinylmagnesium bromide, 1826-67-1.

Solvolysis of 1-Arylethyl Tosylates. Kinetic and Stereochemical Tests for Solvent Participation

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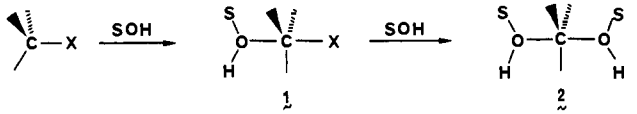
Abstract: Solvolytic studies of the 1-arylethyl tosylates **8a** (Ar = 3-BrC_6H_4), **8b** (Ar = 3-$CF_3C_6H_4$), and **8c** (Ar = 3,5-$(CF_3)_2C_6H_3$) show that in relatively nonnucleophilic solvents all three substrates have polarimetric rates markedly faster than rates of product formation. These products are largely racemic, but solvolysis of **8c** in CF_3CO_2H gives 6% net retention. In the more nucleophilic solvents the rates of product formation are close to the polarimetric rates and the products show extensive inversion of configuration. The results are interpreted in terms of an ion-pair mechanism in which nucleophilic solvent attack on the ion pair plays a major role. In the less nucleophilic solvents this attack is rate limiting, whereas attack of the more nucleophilic solvents is fast and initial ionization is rate limiting. Direct displacement by the solvent could contribute to the reactions in the more nucleophilic solvents but is not required by any of the results. The ion-pair mechanism provides a single consistent explanation for the results in all the solvents with all the substrates, and also readily accommodates a variety of other results in the literature, particularly the findings of oxygen and deuterium scrambling, and elimination during solvolysis.

The classic description of solvolytic reactivity in terms of discrete S_N1 and S_N2 pathways became highly developed in the 1930's and was summarized by Ingold in 1953.[1a] Since that time this area has attracted continuous attention and has been frequently reviewed.[1b,c] Recently the specific role of nucleophilic agents in the rate-limiting transition states in the "borderline" or "combat zone"[1b] region where these mechanisms (designated k_c and k_s, respectively, for solvolysis[1d]) become competitive has been the topic of particularly strong interest. As described below, these developments have prompted us to carry out a systematic test of the simultaneous effect on both reaction rates and product stereochemistry of changing electron demand in 1-arylethyl tosylates, a system of invariant steric requirement which is well suited to elucidate behavior in this region.

Scheme I



A provocative early proposal by Doering and Zeiss[2a] that appeared in 1953 was that pentacovalent intermediates could in-

(1) (a) Ingold, C. K. "Structure and Mechanisms in Organic Chemistry", 1st ed.; Cornell University Press, Ithaca, NY, 1953. (b) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345–375. (c) Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1–67. (d) This classification is due to Winstein; see footnote 2 of Schleyer, P. v. R.; Fry, J. L.; Lam, L. K. M.; Lancelot, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 2542–2544.

(2) (a) Doering, W. v. E.; Zeiss, H. H. *J. Am. Chem. Soc.* **1953**, *75*, 4733–4738. (b) For prior discussions of this idea see: Winstein, S.; Grunwald, E.; Jones, H. W. *Ibid.* **1951**, *73*, 2700–2707, and references therein. See also Streitwieser, A., Jr. "Solvolytic Displacement Reactions"; McGraw-Hill: New York, 1962; pp 66–69.

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